REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

The amendment to claim 5 responds to its self-dependency problem. Claim 1 now is the parent claim. Claim 10 has been revised to respond to the Examiner's statement that no "particular disease state" is recited. The Examiner's comments are not entirely understood. Applicants' use of "treating" was not meant as limiting to the clinical sense of diagnosing a disease and then prescribing a drug response to the diagnosed disease. While it is true that the inventive complex can be so used inasmuch as CoQ-10 has been reported to exert therapeutic effects in several disease states, such as, for example, "cardiovascular disease, periodontal diseases (U.S. Patent No. 6,461,593), high blood pressure, and Parkinson's disease" (application at page 1, ll. 20-21), it is also true that CoQ-10 has been used as nutritional supplement, like general daily supplement for an otherwise healthy population (like a multivitamin). Thus, the inventive complex can be used both as a specific treatment for a diagnosed disease and as a general supplement. In order to clarify claim 10, then, "treating" has been replaced by "administering", based on the application at page 4, ll. 15-17.

Method claims 6 and 10 also have been amended to specify the general method employed by Applicants in preparing the inventive complex. The basis for this claim language can be found at page 5, ll. 16-20.

Claims 21 and 22 are newly presented and provide further detail about the exemplary method of production of the inventive complexes (see the application at p. 5, ll. 17-20). Claims 17 and 18 are cancelled to keep the number of claims at 20. No new fees, then, are due by virtue of the addition of claims 21 and 22.

Inasmuch as no new matter has been added by virtue of these claim amendments, that their entry respectfully is requested.

Sublingual and Oral Ingestion—Claim 5

Claim 5 was faulted, as sublingual and oral ingestion were deemed "redundant". The terms are not redundant. The fact that both routes of administration commence in the mouth or oral cavity is not dispositive of the route of absorption by the body. It is well known that sublingual refers to absorption of a large proportion of the active compound in the buccal cavity, while oral ingestion refers to absorption in the GI tract. Claim 5 goes to formulating the complex to be suitable for "one or more of a topical preparation, a sublingual formulation, or for oral ingestion." Since the route of absorption by the body is

different for each of topic, sublingual, and oral absorption, so too the formulation can be tailored, as is well known in the art.

The Examiner respectfully is requested to withdraw this criticism of and objection to, and/or rejection of claim 5.

The Art Rejections

Claims 1, 4, 5, 6, and 9 stand rejected under the provisions of 35 U.S.C. § 102(b) as being anticipated by Iijima (JP 59-047202). Claims 2, 32, and 4 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel (U.S. Patent No. 5,569,463), Iijima, and Miyao (JP 60-089442). Claims 7, 8, and 9 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel, Iijima, and Miyao.

It is noted that no art rejections have been levied against claims 18-20. With the amendment to independent claim 10, allowance of claims 18-20 respectfully requested.

Applicants respectfully traverse the rejections of the claims and grounds therefor.

The Iijima Citation

Iijima proposes a method for making the CoQ-10/dimethyl-β-cyclodextrin complex containing 1% CoQ-10 in the freeze-dried product. The low level of CoQ-10 makes incorporation of therapeutic concentrations (30-100 mg CoQ-10 per day) in the dosage forms (hard gelatin capsules, tablets) expensive and not viable in the supplement industry. It also is not practical for the tablet or capsule processing, for example it requires 3 g of powder/capsule to obtain a dose 30 mg of CoQ-10.

More importantly, dimethyl-β-cyclodextrin, a chemical derivative of β-cyclodextrin, has entirely different properties than does β-cyclodextrin, in terms of, *inter alia*, its hydrophobicity, solubility, and complexation ability. Dimethyl β-cyclodextrin is soluble in water at room temperature as compared to the sparingly soluble β-cyclodextrin (1.8 g/100 ml water). In general, dimethyl-β-cyclodextrin forms water-soluble inclusion complexes with lipophilic compounds. The CoQ-10/ dimethyl-β-cyclodextrin complex according to Iijima is water soluble, as compared to the water dispersible β- and γ-CoQ-10 complexes of the present invention.

The following publications further illustrate the differences between the two compounds in terms of the properties of the inclusion complexes with different lipophilic compounds.

A. For instance, while β-CD forms an insoluble complex with cholesterol, dimethyl-β-cyclodextrin considerably enhances the aqueous solubility of the sterol up to 10 g/liter. It has been proposed that the nephrotoxicity observed up on parenteral administration of the cholesterol-beta cyclodextrin complex is due to crystallization of the cholesterol in the renal tissue (Frijlink, H.W., Eissens, A.C., Hefting, N.R., Poelstra, K., Lerk, C.F., and Meijer, D.K., "The effect of parenterally administered cyclodextrins on cholesterol levels in the rat", *Pharm. Res.*, 8: 9-16, 1991; Fridrich, R., Mehnert, W., Fromming, K.H., "Studies on the inclusion compound between β-cyclodextrin and cholesterol", In D. Duchene (Ed), 5th *International Symposium on Cyclodextrins*, 1990, pp 299-302, Editions de Sante, Paris; Greenberg-Ofrath, N., Terespolosky, Y., Kahane, I., and Bar, R., "Cyclodextrins as carriers of cholesterol and fatty acids in cultivation of mycoplasmas", *Appl. Envr. Microbiol.*, 59: 547-551, 1993).

B. Ahmed (2001) has reported that the highest aqueous solubility of the piperazine containing drug, Meclizine, was observed on complexation with dimethyl-β-cyclodextrin as compared to α- and β-cyclodextrins. The author attributes the effect to the larger hydrophobic cavity size of dimethyl-β-cyclodextrin (Ahmed, M.O., "Comparison of impact of the different hydrophilic carriers on the properties of piperazine-containing drug", *Eur. J. Pharm. Biopharm.*, 51: 221-225, 2001.

C. Other examples include increase in the solubility of fucosterol on complexation with dimethyl-β-cyclodextrin as compared to β-CD (Acarturk, F., Imai, T., Saito, H., Ishikawa, M., and Otagiri, M., "Comparative study on inclusion complexation of maltosyl-beta-cyclodextrin, heptakis(2,6-di-O-methyl)-beta-cyclodextrin and beta-cyclodextrin with fucosterol in aqueous and solid state", J. *Pharm. Pharmacol.*, 45: 1028-32, 1993); better improvement in the photostability of nifedipine in solid state with dimethyl-β-cyclodextrin compared to beta-cyclodextrin (Bayomi, M.A., Abanumay, K.A., and Al-Angary, A.A., "Effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state", *Int. J. Pharm.*, 243: 107-17, 2002).

Thus, Iijima teaches the skilled artisan only about dimethyl-β-cyclodextrin. The invention is teaching the skilled artisan about α-, β-, and γ-cyclodextrins. These compounds do <u>not</u> have the same chemical properties when it comes to hydrophobicity, solubility, and complexation ability. These properties, however, are the precise properties of interest in making CoQ-10 complexes. In reality, then, Iijima teaches the

skilled artisan nothing about the inventive complexes, nor the unexpected properties, for example achieved by their freeze-dried preparation compared to spray drying, evaporation, *etc.* (see claims 1-5, 16 and 17). Clearly, Iijima totally fails to teach the present invention as required for a § 102(b) rejection. This rejection, then, must be withdrawn.

The Patel Citation

Patel proposes improved delivery systems for pharmaceutical ingredients. The delivery system includes a solid carrier, the solid carrier being formed of different combinations of the pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants, and triglycerides. They mention cyclodextrins as one of the solubilizers among a number of ingredients. The examples illustrate formation of coated beadlets, seal coating, protective coating, or enteric coating of the beadlets, none of which use cyclodextrins or CoQ-10. The examples do not use freeze-drying as a means to obtain dry powders. Patel also does not teach formation of a molecular complexation between CoQ-10 and cyclodextrins or an efficient drying method for any complex.

It is well known in the art that hydrophobic compounds present delivery challenges because of their physicochemical properties. The problems associated with CoQ-10 absorption and the need of developing delivery system also is well known in the industry. Hence, Patel does not offer any specific motivation to produce a CoQ-10 cyclodextrin complex.

It seems to Applicants that the Examiner's only motivation for citing Patel is a vain attempt to reconstruct the invention in hindsight. Of this there can be little doubt.

The Miyao Citation

Miyao teaches the complexation of γ-cyclodextrin with CoQ-10. Miyao uses an aqueous medium, and the mixture is stirred for 67 hours, followed by suction filtration, air drying, and washing with ether, followed by drying. The example indicates ~50% loss in the recovery of the product. It is not obvious from the teachings of Miayao that an economical, commercially viable product can be produced, especially in a cost-conscious supplement industry. Cyclodrextrins in general are expensive and γ-cyclodextrin is the most expensive (currently about $50-$100 per kg). CoQ-10 also is an expensive ingredient (currently about $2800-$5000 per kg) and there is a limited worldwide

production; hence, a 50% loss in the final product recovery is commercially unacceptable.

Miyao teaches two different methods of preparation of its complex: the kneading method and the solution method (see 4th and 5th paragraphs, p. 3, English translation). Now, Miyao's examples show a solution process the includes, *inter alia*, suction filtration, water washing, drying at 70° C, water washing, ether washing, and drying again. Only a 50% recovery of product complex results. Such a process is not amenable to commercial scale-up, in part, due to the low recoveries and use of volatile (potentially explosive) ether wash.

Applicant, on the other hand, uses an aqueous dispersion technique for preparing its complex. Applicant's chosen process employs a cyclodextrin aqueous dispersion homogenized with CoQ-10 (crystals) followed by refrigerated storage to complete the reaction. The complex can be recovered by any conventional technique, such as, freeze-drying resulting in unexpectedly high yields of product complex. Applicant's process is amenable to commercial-scale up and, in fact, already is commercial in this form.

In the present application, then, Applicants have described a highly efficient, commercially viable method for the production of the CoQ-10 inclusion complex with γ- and β-cyclodextrins containing up to about 20%–24% CoQ-10. The process does not include prolonged stirring, suction filtration, or use of highly volatile solvents. The recovery of the product ranges between about 85%–95%, based on the drying method used. With the high prices of the reactants, such high recovery rates are especially valuable and telling of the patentability of the present invention.

More Comments of Preparation Method

It is known that differences in the properties of products can be attributed to the method of preparation of the products, including for cyclodextrins, to wit: strong influence of the preparation method on the physiochemical properties of a binary system of gliquidone and hydroxypropyl-β-cyclodextrin (Sridavi, *et al.*, "Enhancement of dissolution and oral bioavailabilty of gliquidone with hydroxypropyl-beta-cyclodextrin", *Pharmacia*, 2003: 58 (11): 807-10; preparation method plays an important role in dissolution performance of inclusion complexes between nicardipine HCL and β-cyclodextrin (Fernandes, *et al.*, "Physiocochemcial characterization and in vitro dissolution behavior of nicardipine hydrochloride inclusion compounds". *Eur J Pharm Sci.*

2002 Feb; 15(1): 79-88; formation of inclusion complexes of triacetyl-β-cyclodextrin and nicardipine HCL succeeded for a spray-dried product but not for a kneaded product (Fernandes, *et al.*, "Effect of the hydrophobic nature of triacetyl-β-cyclodextrin on the complexation with nicardipine hydrochloride: physicochemical and dissolution properties of the kneaded and spray-dried complex", *Chem Pharm Bull* (Tokyo). 2002 Dec; 50 (12): 1597-602; nature and dissolution factors of cyclodextrin complexes on ibuproxam related to both steric factors and the preparation method (Mura, *et al.*, "Effects of the host cavity size and preparation method on the physicochemical properties of ibuproxam-cyclodextrin systems", *Drug Dev Ind Pharm*. 1999 Mar:25(3) :279-87; method of preparation of albendzole/β-cyclodextrin complexes affects drug release and complex characteristics (Castillo, *et al.*, "Preparation and characterization of albendazole beta-cyclodexrin complexes", *Drug Dev Ind Pharm*. 1999 Dec; 25(12) :12418; both the preparation method and the nature of the carrier play an important role in the performance of a ketoprofen-cyclodextrin binary system (Muza, *et al.*, "Influence of the preparation method on the physicochemical properties of ketoprofen-cyclodextrin binary systems", *Int J Pharm*. 1999 Mar 1; 179(1): 117-28; and the influence of the preparation method was clearly marked for binary systems of econazole with cyclodextrins (Mura, *et al.*, "Influence of the preparation method on the physicochemical properties of binary systems of econazole with cyclodextrins", *Int J Pharm*. 1999 Dec 20; 193(1): 85-95).

Thus, for cyclodextrin and other binary complex systems, it is known in the art that the complex properties, both physical and pharmacological, can be affected by the method of preparation. It is not surprising then that the method of preparation of the inventive CoQ-10/cyclodextrin complexes also affects the bioavailability properties of the complexes. However, without actual experimentation the existence of the affect, the magnitude of the affect, the precise nature of affect, *etc.*, are unknown. In point of fact, there is no literature reference of record that shows this complex, the unexpected bioavailability of the freeze-dried complex and the method of preparation to maximize conversion, as reported by Applicants and as embodied in the claims under examination.

More Comments on the Drying (Recovery) Method

It is well known in the field of cyclodextrins, that for the preparation of solid inclusion complexes from an aqueous system, the water can be removed by evaporation or sublimation, for example by freeze-drying, spray-drying, or any conventional drying

method (Loftsson, T. and Masson, M., "Review-Cyclodextrins in topical drug formulations: Theory and Practice", *Int. J. Pharm*, 225: 15-30, 2001).

Patel describes cryopellitization followed by freeze-drying in a non-specific laundry list of processing methods known in the art for formulations. It is not obvious from their description that a CoQ-10 cyclodextrin inclusion complex can be freeze-dried as part of a commercially viable process.

Iijima describes freeze-drying the aqueous solution of the CoQ-10/dimethyl-beta cyclodextrin complex. However, Iijima does not explore the effects of commercial drying methods on the properties of the CoQ-10 complex. It is well known in the art that the drying methods, such as spray-drying, freeze-drying, or vacuum-drying can affect the final yield, stability, particle size, and dissolution property of the product (see More Comments of Preparation Method discussion, *supra*). Since the cost of drying varies, such information is crucial to developing a cost-effective product, especially in a cost-conscious nutritional supplement industry. Of the three drying methods, freeze-drying is the most expensive, followed by spray-drying, and vacuum-drying.

In the present invention, Applicants unexpectedly found that the method of drying has a significant effect on the bioavailability of CoQ-10 from the complex. Of the three methods of drying, freeze-drying resulted in a highly bioavailable CoQ-10/cyclodextrin complex. However, the other two methods, namely spray-drying or vacuum-drying also can be used if a less expensive product with better bioavailability as compared to crystalline CoQ-10 is required.

Summary

In view of the remarks and claim amendments submitted herewith, allowance of the claims and passage to issue of this application respectfully requested.

Respectfully submitted,

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